Optimizing the dosage of antibiotic for hospitalized pneumonia patients

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ABSTRACT

Optimizing antibiotic therapy should mean prompt achievement and maintenance of optimal exposure of the antibiotic at the site of infection, administered in a timely manner. Basic criteria to be fulfilled are: 1) does the patient really have an infection treatable by antibiotics. 2) are microbial samples warranted before starting treatment, because quantitative assessment is needed for bacteria isolated from the respiratory tract, while bacteria isolated from cerebrospinal fluid, ascites, pleural or articular aspirates are pathogens 3) mono or Combined therapy 4) which administration route? 5) duration of therapy and 6) how to prevent resistance. The interaction of antibiotic – infection site – pathogen and susceptibility – patients pathophysiology - is known as the antimicrobial therapy puzzle. PK-PD knowledge is of paramount importance. High dose, short course regimen with a once daily administration schedule for concentration dependent antibiotics e.g. levofloxacin may yield more rapid bacterial killing and prevention of resistance development, because its efficacy is related to the achievement of high Cmax / MIC ratio (>10) and AUC / MIC ratio, which for gram negative bacteria is > 100-125 and for gram positive bacteria > 30-35. Duration of antibiotic therapy can be as short as 5 days, but can also be determined by procalcitonin levels of < 0.5 mcg / ml or if it has declined > 80% of its peak level.

Keywords: antimicrobial therapy puzzle – PK = pharmacokinetics- PD = pharmacodynamics - Cmax = maximal concentration- MIC = minimal inhibitory concentration – AUC = area undercurve–procalcitonin

OPTIMALISASI TERAPI ANTIBIOTIK PADA PNEUMONIA RAWAT INAP

ABSTRAK

merupakan bagian dari TEKA TEKI terapi antibiotik (antibiotic puzzle)
Kata kunci: PK – PD – Antibiotic Puzzle - MIC

INTRODUCTION

Optimizing antibiotic therapy should mean prompt achievement and maintenance of optimal exposure of the antibiotic at the site of infection. Questions that need to be addressed are:

- Does the patient really have an infection treatable by antibiotics?
- Are microbial samples warranted BEFORE starting therapy?
  - All bacteria isolated from cerebrospinal fluid, ascites, pleural effusions, and articular fluid are pathogens, but quantitative assessment is needed for bacteria isolated from the respiratory tract.
- Mono or combined drug regiments?
- Which administration route?
- Duration of therapy
- How to prevent resistance

The WHO has issued guidelines on the Ideal drug usage in much of the same line:

The CORRECT drug, by the best ROUT, at the right DOSE, at OPTIMUM INTERVALS, for an APPROPRIATE PERIOD, based upon an ACCURATE DIAGNOSIS.

So appropriate antibiotic treatment is summarize in table 1. Implementation of this approach antibiotic treatment guide, brings forth the problem of the” ANTIMICROBIAL THERAPY PUZZLE” requiring knowledge of the Pharmacokinetic and Pharmacodynamic laws (figure 1).
PK-PD parameters of antimicrobials divide antimicrobials into 2 broad categories; 1) concentration dependent antibiotics and time dependent antibiotics (graphically depicted at table 3 and figure 3)

Table 3. PK-PD Clinical outcome

<table>
<thead>
<tr>
<th>S. Pneumoniae (MIC 90)</th>
<th>AUC(24hr) Total</th>
<th>AUC(24hr) MIC 90</th>
</tr>
</thead>
<tbody>
<tr>
<td>LEVO 500</td>
<td>48.0/33.6</td>
<td>34</td>
</tr>
<tr>
<td>LEVO 150</td>
<td>101.0/70.7</td>
<td>71</td>
</tr>
<tr>
<td>MOXI 400</td>
<td>33.8/17.6</td>
<td>70</td>
</tr>
<tr>
<td>GATI 400</td>
<td>33.8/27.0</td>
<td>54</td>
</tr>
<tr>
<td>CIPRO 2</td>
<td>20.2/14.1</td>
<td>7</td>
</tr>
</tbody>
</table>

PK - PD PARAMETERS of antimicrobials

Table 4. Pharmacodynamics activity of Fluoro quinolones against Str. pneumoniae

Table 5: The importance of rapid bactericidal killing
Table 4, shows why Ciprofloxacin is not considered a respiratory quinolone, because its AUC/MIC ratio against 
\( G_r(=) \) cocci is only 7, far below the needed ratio of 30-35, resulting in less bactericidal kill and as such less clinical effectiveness and also resistance (Table 4). The simple explanation for this is that dead bugs do not mutate!!.

**LEVOFLOXACINE 750 mg.**

Although Paul Ehrlich’s maxim of high dose, short course was coined in 1913, a century ago and meant for parasitic infections, Lala Dunbar landmark study in 2002 proved that the same holds true for high dose short course Levofloxacin in Community Acquired Pneumonia (CAP).

At this study, she showed that Levofloxacin 750 mg /OD for 5 days vs Levofloxacin 500 mg/OD for 10 days, gives quicker symptom relief (table 6), with comparable safety (table 7), while exposing the bacterial ecology to 25% less antibiotic and as such decreasing the potential for adaptive resistance.

Simple math tells us that 5 days of 750 mg = 3750 mg, while 10 days of 500 mg is 5000 mg. (Table 6, 7)

Table 6. Quicker symptom relief

<table>
<thead>
<tr>
<th></th>
<th>Levofloxacin 750 mg for 5 days provides greater symptom resolution at day 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SYMPTOMS</td>
</tr>
<tr>
<td></td>
<td>Levofloxacin 750 mg</td>
</tr>
<tr>
<td></td>
<td>Levofloxacin 500 mg</td>
</tr>
<tr>
<td></td>
<td>Levofloxacin 750 mg for 5 days</td>
</tr>
<tr>
<td></td>
<td>Levofloxacin 500 mg for 10 days</td>
</tr>
<tr>
<td>Symptom</td>
<td>Levofloxacin 750 mg for 5 days</td>
</tr>
<tr>
<td>Fever  (painless - previous)</td>
<td>50.0 (35.4)</td>
</tr>
<tr>
<td>Fever (painful)</td>
<td>50.0 (35.4)</td>
</tr>
<tr>
<td>Pulmonary symptoms</td>
<td>90 (57.0)</td>
</tr>
<tr>
<td>Nausea</td>
<td>50 (31.3)</td>
</tr>
<tr>
<td>Diaphoresis</td>
<td>70 (35.1)</td>
</tr>
<tr>
<td>Chills</td>
<td>70 (35.1)</td>
</tr>
<tr>
<td>Cough</td>
<td>70 (35.1)</td>
</tr>
</tbody>
</table>

*Table 6. Quicker symptom relief*

Table 7. Comparable safety 750 mg OD -500 mg OD

**DURATION of ANTIBIOTIC THERAPY IN CAP**

There are several suggestions, but no precise guidelines, all empirical

- IDSA (Infectious diseases society of America): 72 hrs afebrile
- Canadian infectious and thoracic Society: 1-2 wks
- BTS (British Thoracic Society): 7-21 days, subj. to clin.judg.
- ATS (American Thoracic Society): 7-14 days for hosp.5-7 d out pat.

Using PROCALCITONIN to customized duration of antibiotic therapy, when its concentration is less than 0.5 ng/ml or has decreased by more than 80% from its peak concentration, antibiotics can be stopped, but vigilance must be maintained to detect recurrence.

**SUMMARY HIGH DOSE SHORT COURSE LEVOFLOXACIN IN CAP:**

High dose, short course regimen, with a once daily administration schedule may yield...
more rapid bacterial killing and prevention of resistance development, because its efficacy is related to the achievement of high Cmax / MIC ratio (>10) and auc / mic ratio, which for gram (-) bacteria should be > 100-125 and for gram (+) > 30-35

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